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(54) Title: TRANSITION METAL MEDIATED PROCESS

(57) Abstract: This invention relates to a transition metal mediated process for the preparation of optionally substituted 2-amino-benzoxazoles and or 2-amino-benzimidazoles, which are useful as therapeutic agents or as intermediates in the synthesis of therapeutic agents.



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TRANSITION METAL MEDIATED PROCESS

CROSS-REFERENCE TO RELATED APPLICATION

5 This application claims priority to US provisional application no. 60/278,072, filed 22 March 2001.

BACKGROUND OF THE INVENTION

Substituted or unsubstituted 2-amino-benzoxazoles and 2-amino-benzimidazoles
10 are present in certain commercial compounds, such as therapeutic drugs. These compounds are known to have biological activity against a number of biological targets, for example, and not exclusively including, inhibitors or modulators of histamine receptors (for example see: Yanni *et al.*, World Pat. No. 9413299-A1), rotamase (Wythes *et al.*, World Pat. No. 2000005231-A1), type 2 helper T cell function (Japan
15 Pat. Appl. 10330369-A), inosine-5'-monophosphate dehydrogenase (Saunders *et al.*, World Pat. No. 9840381-A1), G-protein coupled receptors (Sato *et al.*, European Pat. No. 806419-A1 and Biol. Pharm. Bull., **20**(7), 752-755 (1997)), fibrinogen (Casanova *et al.*, Diabetes, **46**, Suppl. 1, 116A (1997)), peroxisome proliferator activated receptors (Smith, World Pat. No. 9725042-A1), calpain (Japan Pat. Appl. 08183771-A), HIV
20 reverse transcriptase (Hoffman *et al.*, U.S. Pat. No. 5308854-A), leukotriene function (Farina *et al.*, J. Pharmacol. Exp. Ther., **271** (3), 1418-1426, (1994), Pal *et al.*, European Pat. No. 657451-A2), and integrins (Clark *et al.*, World Pat. No. 200049005-A1, 200050380-A1, 200061580-A1, 200068213-A1 and Brittain *et al.*, World Pat. No. 200005223-A2).

25 The preparation of substituted 2-amino-benzoxazoles or 2-amino-benzimidazoles has been achieved *via* a number of synthetic strategies. These include cyclodesulfurization of a substituted *N*-(2-hydroxyphenyl)- or a *N*-(2-aminophenyl)-thiourea in the presence of either mercuric oxide (for example, Garin *et al.*, J. Heterocyclic Chem., **27** (2), 221 (1990), and Perkins *et al.*, Tet. Lett., **40** (6), 1103-1106,
30 (1999)), nickel dioxide (*e.g.* Ogura *et al.*, Chem. Pharm. Bull., **29**(6), 1518 (1981)), potassium superoxide (*e.g.* Sung *et al.*, Chem. Lett., (8), 1291-1294 (1986)), *N,N'*-dicyclohexylcarbodiimide (*e.g.* German Patent No. DE 3006671, Saunders *et al.*, World Pat. No. 9840381-A1) sodium hypochlorite and a phase transfer catalyst (Dehmlow *et*

al., Israel J. Chem., 26, 219 – 221 (1985)) or lead oxide. In one example, the thioureas can be prepared from the corresponding isothiocyanate and substituted 2-hydroxyaniline. Subsequently, the concomitant ring closure with mercuric oxide to afford the substituted 2-aminobenzoxazole occurs in a one-pot two-step procedure (Garin *et al.*, *J. Heterocyclic Chem.*, **28**, 359–363 (1991)). Polyphosphate ester has also been used to perform a similar ring closure reaction on *N*-(2-hydroxyphenyl)ureas (Katsura *et al.*, *Chem. Pharm. Bull.*, **40** (6), 1424 – 1438 (1992)). Displacement of a 2-chloro (*J. Med. Chem.*, **41** (16), 3015-3021 (1998)), 2-aryloxy (Kover *et al.*, *Synthesis*, 1124-1126 (1994)) or a 2-thio (*Pharmazie*, 1997, 52(8), 585-589) substituent on the benzoxazole or benzimidazole with nitrogen nucleophiles, to afford the 2-amino variant, has also been reported.

The main disadvantages of utilizing these methods are as follows:

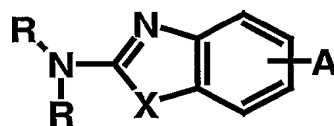
- a). Often the procedures require a dedicated multi-step synthesis of an intermediate thiourea or a 2-substituted benzoxazole or benzimidazole. In the majority of the procedures these intermediates often require a dedicated work-up and purification prior to the final step in the synthesis of the desired product.
- b). Many of the reactions require high temperatures (> 100 °C) and the presence of high boiling solvents in order to proceed to completion. This can be detrimental when the cyclodesulfurization step is in competition with other chemical transformations that prefer higher reaction temperatures.
- c). A number of the reagents present toxicological and physical hazards. For example, mercuric oxide is highly toxic (oral LD₅₀ = 18 mg/kg in rats) and potassium superoxide presents an explosive risk in the presence of minor organic contaminants (Bretherick, L., *Chem. Br.*, **14**(9), 426 (1978)).
- d). In some cases, the removal of the reagent byproducts, *e.g.* in reactions using *N,N'*-dicyclohexylcarbodiimide or polyphosphate ester, can be problematic, labor intensive and unsuitable for scale-up.

SUMMARY OF THE INVENTION

In one embodiment, the present invention is directed to a method of making an optionally substituted 2-amino-benzoxazole or 2-amino-benzimidazole which comprises reacting a corresponding optionally substituted *N*-(2-hydroxyphenyl)thiourea or *N*-(2-aminophenyl)thiourea, respectively, with a transition metal in its I or II oxidation state,

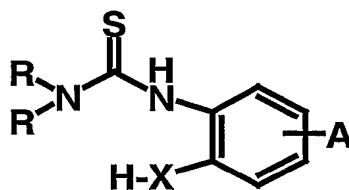
in the presence or absence of a base to obtain the optionally substituted 2-amino-benzoxazole or 2-aminobenzimidazole.

In another embodiment, the present invention is directed to a process for the synthesis of a compound of formula (II),



(II)

comprising the step of reacting a compound of formula (I),



(I)

with a transition metal in its I or II oxidation state and optionally a base to obtain the compound of formula (II);

wherein:

A represents one or more substituents, each independently selected from the group consisting of hydrogen, halogen, -CN, -NO₂, -C(O)OH, -C(O)H, and -OH, or is an optionally substituted moiety each independently selected from the group consisting of -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heterocyclyl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heterocyclyl, carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, alkyl, cycloalkyl, alkoxy, aryl, heterocyclyl, alkenyl, alkynyl, aryloxy, heterocycliloxy, heterocyclylalkoxy, arylalkoxy, alkyl-S(O)_p-, alkyl-S-, aryl-S, heterocyclyl-S-, aryl-S(O)_p-, heterocyclyl-S(O)_p-, arylalkyl, heterocyclylalkyl, cycloalkylalkyl, amino, aminoalkyl, amido, -Z¹-C(O)N(R¹)₂, -Z¹-N(R¹)-C(O)-Z², -Z¹-N(R¹)-S(O)₂-Z², -Z¹-N(R¹)-C(O)-N(R¹)-Z², and CH₂OR²;

where R¹ for each occurrence is independently H, or optionally substituted alkyl, heterocyclyl, aryl, aralkyl or heterocyclylalkyl;

p is 1 or 2;

R^2 for each occurrence is independently hydrogen, or optionally substituted alkyl, aryl, heterocyclyl, $-\text{CH}_2-\text{NR}^d\text{R}^e$, $-\text{W}-(\text{CH}_2)_t-\text{NR}^d\text{R}^e$, $-\text{W}-(\text{CH}_2)_t-\text{O}-\text{alkyl}$, $-\text{W}-(\text{CH}_2)_t-\text{S}-\text{alkyl}$, or $-\text{W}-(\text{CH}_2)_t-\text{OH}$;

R^d and R^e for each occurrence are independently H, alkyl, alkanoyl or SO_2 -alkyl; or R^d , R^e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

W is a covalent bond, O, S, S(O), S(O)₂ or NR^f , where R^f is H or alkyl;

t for each occurrence is independently an integer from 2 to 6;

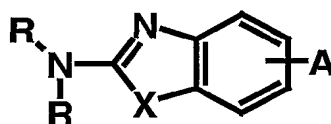
Z^1 is a covalent bond or alkyl;

Z^2 is an optionally substituted alkyl, aryl, heterocyclyl, arylalkyl, or heterocyclylalkyl;

R for each occurrence is independently hydrogen or silyl or is independently an optionally substituted moiety selected from the group consisting of alkyl, arylalkyl, heterocyclylalkyl, aryl, heterocyclyl, cycloalkyl, and cycloalkylalkyl; or each R is taken together with the nitrogen atom to which they are attached to form an optionally substituted 5- or 6-membered ring optionally having one or more other heteroatoms selected from the group consisting of N, O and S; and

X is O, NH, N-alkyl, N-cycloalkyl, N-arylalkyl, N-heterocyclylalkyl, N-sulfonyl, N-carboxyl, N-aryl, or N-heterocyclyl wherein the group attached to the nitrogen is optionally substituted with one or more substituents.

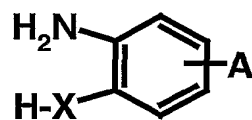
In another embodiment, the present invention is directed to a process for the synthesis of a compound of formula (II),



(II)

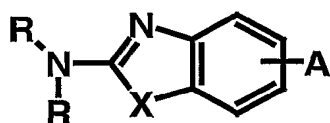
which comprises reacting an isothiocyanate, an optionally substituted 2-(X)-aniline, a transition metal in its I or II oxidation state and optionally a base, to obtain a compound of formula (II), wherein the variables are as defined hereinabove.

In a preferred embodiment of the immediately foregoing embodiment, the isothiocyanate is of the formula R-NCS and the optionally substituted aniline is of the formula



(I)

In another embodiment, the present invention is directed to a process for the synthesis of a compound of formula (II),



(II)

comprising the steps of:

- 10 forming an isothiocyanate *in situ* by reacting an amine or an aniline with a reagent having a thiocarbonyl moiety and which is capable of a double nucleophilic attack at the carbon of the thiocarbonyl moiety to yield the isothiocyanate; and reacting the isothiocyanate with an optionally substituted 2-(X)-aniline, a transition metal in its I or II oxidation state and optionally a base, to obtain a compound of formula (II),
- 15 wherein the variables are as defined hereinabove.

A preferred embodiment of any of the present inventions is where the base is present in the reaction.

A preferred embodiment of any of the present inventions is where the transition metal is Cr, Mn, Fe, Co, Cu or Zn, or a combination thereof.

- 20 A preferred embodiment of any of the present inventions is where the transition metal is a corresponding salt or a combination of salts.

A preferred embodiment of any of the present inventions is where, the transition metal salt is one or more copper salts.

- 25 A preferred embodiment of any of the present inventions is where the base is an one or more organic bases.

A preferred embodiment of any of the present inventions is where the organic base is triethylamine or ammonia, or a combination thereof.

A preferred embodiment of any of the present inventions is where the transition metal salt is copper (II) sulfate, anhydrous copper (II) sulfate or copper (I) chloride or a
5 combination thereof.

A preferred embodiment of any of the present inventions is where the base is one or more inorganic base.

A preferred embodiment of any of the present inventions is where the inorganic base is sodium hydroxide, sodium hydrogen carbonate or cesium carbonate, or a
10 combination thereof.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a novel transition metal mediated process for the preparation of optionally substituted 2-amino-benzoxazoles and 2-amino-benzimidazoles. In one aspect, the process is useful for preparing optionally substituted
15 2-amino-benzoxazoles or 2-amino-benzimidazoles which are useful as drugs such as kinase inhibitors or as intermediates for making other compounds that are useful as drugs.

The invention particularly relates to the use of a transition metal, preferably as a salt, for example copper salts, particularly anhydrous copper (II) sulfate, optionally in
20 the presence of a base, *e.g.* triethylamine, and preferably in the presence of the base, as highly active reagents for the desulfurization and concomitant ring closure of an optionally substituted *N*-(2-hydroxyphenyl)thioureas or *N*-(2-aminophenyl)thioureas to afford the corresponding optionally substituted 2-amino-benzoxazole or 2-amino-benzimidazole, respectively.

The process offers the advantages that it can be performed under mild temperatures, for example about 20 °C to 60 °C, however higher and lower temperatures can be used, and in a range of organic solvents, for example tetrahydrofuran, acetonitrile and dichloromethane. The substituted *N*-(2-hydroxyphenyl)thioureas or *N*-(2-aminophenyl)thioureas can be prepared from the corresponding isothiocyanate and
25 either the substituted or unsubstituted 2-amino phenol or the substituted or unsubstituted phenylenediamine, respectively, in a single-pot reaction.
30

In a variation of the above procedure, the isothiocyanate can be formed *in situ* in the reaction vessel from either an amine or an aniline using reagents known in the art for

making isothiocyanates, for example, and not exclusively including, 1,1'-thiocarbonyldi-2-(1*H*)pyridone, 1,1'-thiocarbonyldiimidazole or thiophosgene. Once this reaction is complete, the remaining reagents may be added to the same reaction vessel according to the general procedure described herein to afford the optionally substituted 2-amino-
5 benzoxazole or 2-amino-benzimidazole in a single pot procedure.

Additionally, the copper salts and a base can be added, simultaneously, with the isothiocyanate and the substituted aniline to afford the optionally substituted 2-amino-benzoxazole and 2-amino-benzimidazole in a one-pot, one-step procedure.

Copper salts offer the advantages of low cost and low toxicity, for example,
10 copper (II) sulfate has an oral LD₅₀ in rats of 300 mg/kg.

The following terms have the noted meanings as used herein

"Alkyl" refers to a saturated aliphatic hydrocarbon, or an aliphatic group having one or more unsaturated groups, including straight-chain and branched-chain groups. Preferred straight chain and branched alkyl groups include C₁-C₈ alkyl groups.

15 "Alkenyl" refers to an aliphatic hydrocarbon having at least one double bond, including straight-chain and branched-chain groups. Preferred straight chain and branched alkenyl groups include C₁-C₈ alkyl groups.

"Alkynyl" refers to an aliphatic hydrocarbon having at least one triple bond, including straight-chain and branched-chain groups. Preferred straight chain and
20 branched alkynyl groups include C₁-C₈ alkyl groups.

"Alkoxy" refers to an "O-alkyl" group, where "alkyl" is defined as described above.

"Cycloalkyl" refers to mono-, bi- and tri-carbocyclic groups having 3 to 12 carbon atoms, preferred cycloalkyl groups have 3 to 6 ring carbon atoms.

25 "Heterocyclyl" means an optionally substituted mono- or bi-cyclic aromatic or non-aromatic heterocycle in which the heterocycle contains 1, 2, 3 or 4 hetero atoms selected from nitrogen, sulphur or oxygen. The heterocyclyl group may be attached through a carbon atom or a hetero atom. Suitable heterocyclyl groups include but are not restricted to 1,3-dioxolanyl, 1,4-dioxolanyl, morpholinyl, piperidinyl, piperazinyl,
30 thiomorpholinyl, 3H-indolyl, 4H-quinoliziny, 2-imidazoliny, imidazolidiny, quinuclidiny, 2-pyrazoliny, pyrazolidiny, 2H-pyrany, 4H-pyrany, 1,4-dithianyl, 1,3,5-trithianyl, tetrahydrofurany, pyrrolidinyl, pyrrolyl, imidazolyl, isothiazolyl, pyrazolyl, thiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyridazinyl,

pyrimidinyl, pyrazinyl, benzimidazolyl, quinolinyl, isoquinolinyl, indazolyl, furanyl, 2,3,4,5-tetrahydrofuranyl, thienyl, benzofuranyl, indoliziny, imidazopyridinyl, isoxazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, benzothiazolyl, benzothienyl, purinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,5-triazinyl, cinnolinyl, phthalazinyl, 5 quinazolinyl, quinoxalinyl, 1,8-naphthypyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl and phenoxazinyl.

“Aryl” means a mono-, bi- or tri-cyclic aromatic group. Suitable aryl groups include phenyl, indenyl, naphthyl, azulenyl, flourenyl and anthracenyl.

The term “optionally substituted” means that the moiety that it modifies can be substituted with any one or more substituents known to one skilled in the art that results in a chemically stable molecule. Since the processes of the present invention is not limited by the substituents attached to the starting material isothiocyanate and 2-(X)-aniline, all such compounds are within the scope of the present invention. Preferred substituents within the “optionally substituted” non-exclusively includes: halogen, -CN, 15 -NO₂, -C(O)OH, -C(O)H, and -OH, or is an optionally substituted moiety each independently selected from the group consisting of -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heterocyclyl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heterocyclyl, carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, alkyl, cycloalkyl, alkoxy, aryl, heterocyclyl, alkenyl, alkynyl, aryloxy, heterocycliloxy, 20 heterocyclylalkoxy, arylalkoxy, alkyl-S(O)_p-, alkyl-S-, aryl-S, heterocyclyl-S-, aryl-S(O)_p-, heterocyclyl-S(O)_p-, arylalkyl, heterocyclylalkyl, cycloalkylalkyl, amino, aminoalkyl, amido, -Z¹-C(O)N(R¹)₂, -Z¹-N(R¹)-C(O)-Z², -Z¹-N(R¹)-S(O)₂-Z², -Z¹-N(R¹)-C(O)-N(R¹)-Z², and CH₂OR²;

where R¹ for each occurrence is independently H, or optionally substituted alkyl, 25 heterocyclyl, aryl, aralkyl or heterocyclylalkyl;

p is 1 or 2;

R² for each occurrence is independently hydrogen, or optionally substituted alkyl, aryl, heterocyclyl, -CH₂-NR^dR^e, -W-(CH₂)_t-NR^dR^e, -W-(CH₂)_t-O-alkyl, -W-(CH₂)_t-S-alkyl, or -W-(CH₂)_t-OH;

30 R^d and R^e for each occurrence are independently H, alkyl, alkanoyl or SO₂-alkyl; or R^d, R^e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

W is a covalent bond, O, S, S(O), S(O)₂ or NR^f, where R^f is H or alkyl;

t for each occurrence is independently an integer from 2 to 6;

Z^1 is a covalent bond or alkyl; and

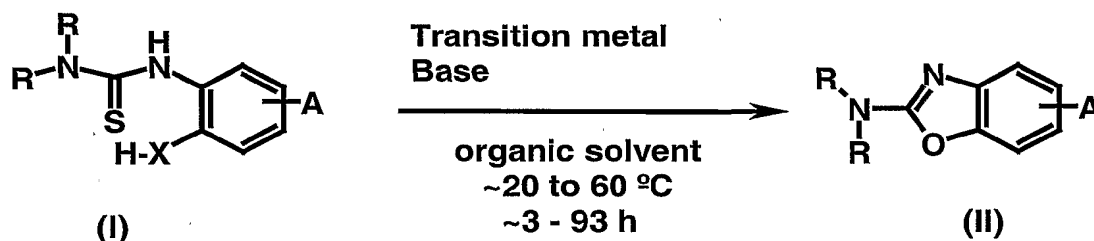
Z^2 is an optionally substituted alkyl, aryl, heterocyclyl or arylalkyl, or heterocyclylalkyl.

- 5 Unless otherwise specified, all starting materials and solvents were obtained from commercially available sources and were used without further purification. Further starting materials can be synthesized according to known literature methods or according to the skills of one of ordinary skill in the art.

All articles and patents cited in the present application are incorporated herein by
10 reference in their entirety.

One embodiment of a process of the present invention is described in Scheme 1.

Scheme 1.



wherein the variables are as defined hereinabove.

15

Transition metal = Cr, Mn, Fe, Co, Cu or Zn, or a combination of the aforementioned metals, wherein the metal is in its I or II oxidation state. Preferred are the salts of the foregoing metals or combination thereof.

Base = an organic base, for example, triethylamine or ammonia, or an inorganic base,
20 for example, sodium hydroxide or sodium hydrogen carbonate.

The starting thiourea (I) is subjected to cyclodesulfurization using a transition metal, as noted above, preferably in the form of a salt, for example anhydrous copper (II) sulfate or copper (I) chloride, and an organic or inorganic base, preferably an organic base, for example triethylamine, to afford the corresponding optionally
25 substituted 2-aminobenzoxazoles or 2-aminobenzimidazoles (II). The ring closure reaction can take place in a range of organic solvents, preferably in one or a mixture of non-protic solvents, in particular tetrahydrofuran, acetonitrile, and dichloromethane, and at mild temperatures, typically about 20 °C to 60 °C. The reaction provides good to excellent yields of the desired product within this temperature range. However,

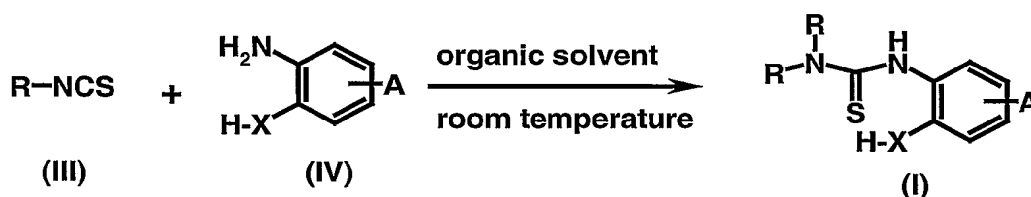
temperatures outside of the range may be utilized to obtain the desired product. In general, the reaction proceeds faster at higher temperatures within the range of 20 °C to 60 °C.

The reaction performs efficiently in the presence or absence of silica. Further,
5 reducing the stoichiometry of the transition metal, for example 1.1 equivalents, has no affect on the reaction yield yet significantly helps facilitate the reaction work-up and purification procedures.

In addition to salt forms of a transition metal used in a process of the present invention, other forms of transition metals that can be used in a process of the present
10 invention include complexes of a transition metal and a resin or support bound transition metal. An example of a transition metal complex is [Cu(OH)(*N,N,N',N'*-tetramethylethylenediamine)]₂Cl₂ (Collman et al; Org. Lett, **9**(2), 1233-1236, (2000) and J. Org. Chem., **66**, 1528, (2001)) which can be used as a catalyst for the cyclodesulfurization reaction. For an example of a transition metal such as a copper
15 reagent bound to a solid support or polymer, see: Amaratunga et al., Polym. Prepr., 22(1), 151-2, (1981), Kalalova et al., Collect. Czech. Chem. Commun., 48(7), 2021-7, (1983), and Koning et al., React. Polym., Ion Exch., Sorbents 4(4), 293-309, (1986).

The following Scheme 2 illustrates a method for obtaining an intermediate thiourea of formula (I), where the variables are as defined hereinabove and one R is
20 hydrogen:

Scheme 2.



The thioureas (I) can be prepared from the corresponding isothiocyanate (III) and the 2-substituted aniline (IV). Once the thiourea (I) formation is complete, the reaction illustrated in Scheme 1 can be carried out in the same reaction vessel without having to isolate and purify the thiourea (I). For example by adding a transition metal as described hereinabove, such as anhydrous copper (II) sulfate, or copper (I) chloride, and a base, such as triethylamine, to the crude reaction mixture to afford the corresponding optionally substituted 2-amino-benzoxazole or 2-amino-benzimidazole product of formula (II) in a one-pot, two-step procedure. Thus, the intermediate thiourea (I) does not require isolation or purification during this process.

In another embodiment, a transition metal, preferably a salt thereof, for example copper (II) sulfate, or copper (I) chloride, and a base, *e.g.* triethylamine, can be added simultaneously with the isothiocyanate (III) to a 2-optionally substituted aniline (IV) to afford the corresponding optionally substituted 2-amino-benzoxazole or 2-amino-benzimidazole of formula (II), in a one-pot, one-step procedure.

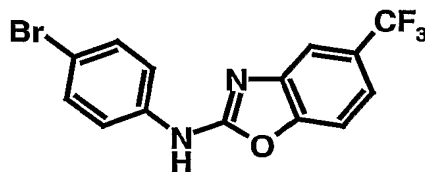
Furthermore, a starting material isothiocyanate can be formed *in situ* in the reaction vessel from either an amine or an aniline using reagents known in the art, for example, and not exclusively including, 1,1'-thiocarbonyldi-2-(1*H*)pyridone, 1,1'-thiocarbonyldiimidazole or thiophosgene. Once this reaction is complete, the remaining reagents may be added to the same reaction vessel according to the general procedure described herein to afford the corresponding optionally substituted 2-amino-benzoxazole or 2-amino-benzimidazole in a single pot procedure.

An optionally substituted 2-amino-benzoxazole or 2-amino-benzimidazole of formula (II) can be isolated according to standard methods known in the art. For example, by removing the reaction solvent *in vacuo*, dissolving the residue in an organic solvent, for example, ethyl acetate or dichloromethane, and washing with aqueous solutions, known to those skilled in the art, which can sequester the transition metal, such as a copper salt, for example, these include: aqueous solutions of ammonia,

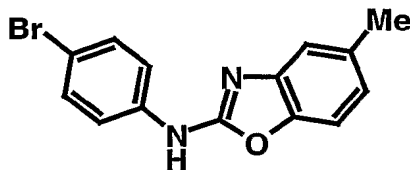
picolinic acid, oxalic acid, pyridine, and ethylenediaminetetraacetic acid (EDTA). The product can then be subjected to additional purification, using methods such as recrystallization or chromatography, as desired. In those embodiments of the present invention wherein a complex of a transition metal or a transition metal bound to a solid support is used in the reaction, various isolation and purification methods for obtaining the desired optionally substituted 2-amino-benzoxazole or 2-amino-benzimidazole are known to those skilled in the art.

The following examples serve to illustrate the present invention and are not to be construed as limiting the scope of the present invention to the embodiments so exemplified. Nuclear magnetic resonance (NMR) were measured on a 400 MHz Bruker instrument and peak positions are expressed in parts per million (ppm). The peak shapes are denoted as follows: *s*, singlet; *d*, doublet; *dd*, double doublet; *t*, triplet; *hept*, heptet; *m*, multiplet. “*J*” denotes the splitting constant which is expressed in Hertz (Hz).

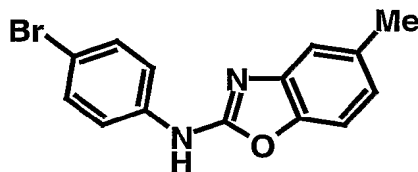
Example 1. N2-(4-Bromophenyl)-5-trifluoromethyl-1,3-benzoxazol-2-amine



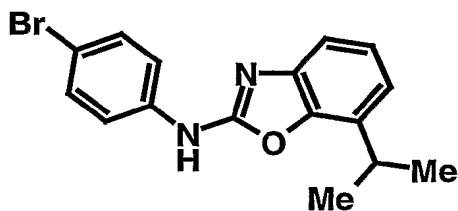
4-Bromophenyl isothiocyanate (1.667 g, 7.785 mmol) was added to a solution of 2-amino-4-trifluoromethylphenol (1.379 g, 7.785 mmol) in tetrahydrofuran (THF) (100 mL) and the reaction was stirred at room temperature for about 16 hours then at about 50 °C for about another 5 hours. Copper (I) chloride (0.771 g, 7.785 mmol) and triethylamine (1.08 mL, 7.785 mmol) were added, and the mixture was stirred at room temperature for about 72 hours and then at about 50 °C for about another 18 hours. Additional copper (I) chloride (0.385 g) was added and the reaction was stirred at about 60 °C for about another 2 hours. The reaction was concentrated under reduced pressure, dissolved in methanol (200 mL), filtered through a pad of diatomaceous earth and the solvent removed *in vacuo* to afford *N2-(4-bromophenyl)-5-trifluoromethyl-1,3-benzoxazol-2-amine* as a brown solid (3.90 g, 140 % of theory); RP-HPLC Rt 17.627 min, 77 % purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Waters Deltapak® C18, 300 Å, 5 μ m, 150 x 3.9 mm column); and *m/z* 354.9 and 356.9 (*M-H*⁻).

Example 2. N2-(4-Bromophenyl)-5-methyl-1,3-benzoxazol-2-amine

4-Bromophenyl isothiocyanate (2.0 g, 9.34 mmol) was added to a solution of 2-amino-4-methylphenol (1.15 g, 9.34 mmol) in acetonitrile (100 mL) and the reaction
5 was stirred at room temperature for about 16 hours. The formation of the intermediate *N*-(4-bromophenyl)-*N'*-(2-hydroxy-5-methylphenyl)thiourea was complete, as analyzed by RP-HPLC Rt 13.010 min, 98% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak® C18, 300 Å, 5 μ m, 150 x 3.9 mm column). Copper (I) chloride (0.925 g,
10 9.34 mmol) and triethylamine (1.29 mL, 9.34 mmol) were added, and the mixture was stirred at room temperature for about 6 days. The reaction was concentrated under reduced pressure, dissolved in methanol (200 mL), filtered through a pad of diatomaceous earth and the solvent removed *in vacuo* to afford a brown solid. The solid was dissolved in dichloromethane (200 mL), washed with water (2 x 200 mL), dried
15 over anhydrous sodium sulfate and absorbed onto silica (10 mL). The product was purified by chromatography through a silica pad using 10% ethyl acetate in *n*-heptane as the eluent to afford *N*2-(4-bromophenyl)-5-methyl-1,3-benzoxazol-2-amine as a yellow solid (0.30 g, 11 %); RP-HPLC Rt 16.451 min, 95 % purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at
20 1mL/min; λ = 254 nm; Deltapak® C18, 300 Å, 5 μ m, 150 x 3.9 mm column); and *m/z* 302.9 and 304.9 (*MH*⁺).

Example 3. N2-(4-Bromophenyl)-5-methyl-1,3-benzoxazol-2-amine

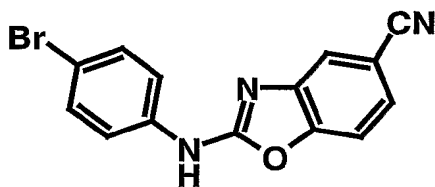
4-Bromophenyl isothiocyanate (2.0 g, 9.34 mmol) was added to a solution of 2-amino-4-methylphenol (1.15 g, 9.34 mmol) in tetrahydrofuran (100 mL) and the reaction
5 was stirred at room temperature for about 16 hours. The formation of the intermediate *N*-(4-bromophenyl)-*N'*-(2-hydroxy-5-methylphenyl)thiourea was complete, as analyzed by RP-HPLC Rt 12.973 min, 88% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak® C18, 300 Å, 5 μ m, 150 x 3.9 mm column). Anhydrous copper (II) sulfate
10 (14.06 g, 88.10 mmol), silica gel (14.06 g), and triethylamine (1.3 mL, 9.34 mmol) were added, and the mixture was stirred at room temperature for about another 72 hours. The reaction was filtered through a pad of diatomaceous earth washed with diethyl ether (3 x 100 mL) and the combined filtrate was concentrated under reduced pressure to afford *N2*-(4-bromophenyl)-5-methyl-1,3-benzoxazol-2-amine as a brown solid (2.70 g, 95 %);
15 RP-HPLC Rt 16.433 min, 99 % purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak® C18, 300 Å, 5 μ m, 150 x 3.9 mm column); and ¹H NMR (400 MHz, *d*₆-DMSO) 2.37 (3H, *s*), 6.94 (1H, *d*, *J* 8.1Hz), 7.27 (1H, *s*), 7.36 (1H, *d*, *J* 8.1Hz), 7.54 (2H, *d*, *J* 8.4 Hz), 7.72 (2H, *d*, *J* 8.4 Hz), and 10.72 (1H, *s*).

Example 4. N2-(4-Bromophenyl)-7-isopropyl-1,3-benzoxazol-2-amine

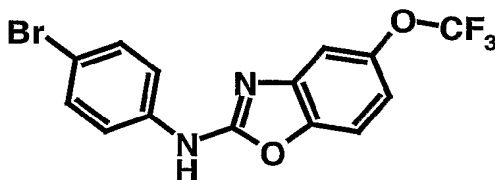
4-Bromophenyl isothiocyanate (0.50 g, 2.34 mmol) was added to a solution of 2-amino-6-isopropylphenol (0.354 g, 2.34 mmol) in tetrahydrofuran (35 mL) and the reaction was stirred at room temperature for about 3 hours. Anhydrous copper (II)
25 sulfate (3.361 g, 21.06 mmol), silica gel (3.361 g), and triethylamine (0.33 mL, 2.34 mmol) were added, and the mixture was stirred at room temperature for about 18 hours. The reaction was filtered through a pad of diatomaceous earth, the diatomaceous earth

was washed with diethyl ether (3 x 50 mL), and the combined filtrate was concentrated under reduced pressure and the resulting brown solid was purified by column chromatography through a silica pad using neat ethyl acetate as the eluent to afford *N*2-(4-bromophenyl)-7-isopropyl-1,3-benzoxazol-2-amine as a light brown solid (0.70 g, 91 %); RP-HPLC Rt 18.066 min, 86% purity (5% to 85% acetonitrile/0.1M ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak® C18, 300 Å, 5 μ m, 150 x 3.9 mm column); ^1H NMR (400 MHz, d_6 -DMSO) 1.34 (6H, *d*, *J* 6.9 Hz), 3.25 (1 H, *hept*, *J* 6.9 Hz), 7.02 (1H, *d*, *J* 7.3 Hz), 7.16 (1H, *t*, *J* 7.7 Hz), 7.29 (1H, *dd*, *J* 7.7 and 1.1 Hz), 7.55 (2H, *dd*, *J* 6.9 and 2.1 Hz), 7.74 (2H, *dd*, *J* 6.9 and 2.1 Hz) and 10.807 (1H, *s*).

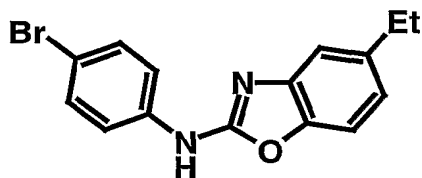
Example 5. *N*2-(4-Bromophenyl)-5-cyano-1,3-benzoxazol-2-amine



4-Bromophenyl isothiocyanate (2.93 g, 0.0137 mol) was added to a solution of 3-amino-4-hydroxybenzonitrile (1.84 g, 0.0137 mol) in acetonitrile (140 mL) at room temperature. The mixture was stirred for about 16 hours prior to the addition of copper (I) chloride (1.36 g, 0.0137 mol) and triethylamine (1.9 mL, 0.0137 mol). The mixture was stirred for about another 16 hours and the solvent was removed under reduced pressure. The solid was dissolved in methanol (100 mL), filtered through a pad of diatomaceous earth, and washed with additional methanol (2 x 50 mL). The brownish filtrate was left to stand at about 4 °C for about 3 days and the resulting precipitate was collected by filtration to afford *N*2-(4-bromophenyl)-5-cyano-1,3-benzoxazol-2-amine (2.4 g, 0.0076 mol, 55 %); RP-HPLC Rt 11.1 min, 92 % purity (Delta Pak C18, 5 μ m, 300 Å, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min); and ^1H NMR (400 MHz, d_6 -DMSO) 7.59 (3H, *m*), 7.72 (3H, *m*), 7.97 (1H, *s*), and 11.12 (1H, *s*).

Example 6. N2-(4-Bromophenyl)-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine

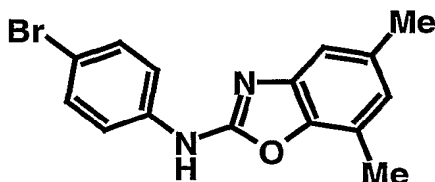
4-Bromophenyl isothiocyanate (1.00 g, 0.0047 mol) was added to a solution of 2-amino-4-(trifluoromethoxy)phenol (0.90 g, 0.0047 mol) in tetrahydrofuran (60 mL) at room temperature. The mixture was stirred for about 16 hours prior to the addition of anhydrous copper (II) sulfate (7.10 g, 0.0443 mol), triethylamine (0.67 mL, 0.0047 mol) and silica gel (8.50 g). The mixture was stirred for about another 4 hours and the solvent was then removed under reduced pressure. The residue was purified by column chromatography through a silica pad using 25 % ethyl acetate in *n*-heptane as the eluent. The resulting orange solid was further purified by chromatography over silica gel; using a 0 % to 25 % ethyl acetate in *n*-heptane gradient as the eluent. The solid was triturated with *n*-heptane to give *N2*-(4-bromophenyl)-5-(trifluoromethoxy)-1,3-benzoxazol-2-amine (0.90g, 0.0024 mol, 51 %); RP-HPLC Rt 12.2 min, 99 % purity (DeltaPak® C18, 5 µm, 300 Å, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min); and *m/z* 373 and 375 (*MH*⁺).

Example 7. N2-(4-Bromophenyl)-5-ethyl-1,3-benzoxazol-2-amine

4-Bromophenyl isothiocyanate (1.40 g, 0.0065 mol) was added to a solution of 2-amino-4-ethylphenol (0.89 g, 0.0065 mol) in tetrahydrofuran (80 mL) at room temperature. The mixture was stirred for about 2 hours prior to the addition of anhydrous copper (II) sulfate (6.2 g, 0.039 mol), triethylamine (0.9 mL, 0.0065 mol) and silica gel (11.7 g). The mixture was stirred for an another 4 hours and the solvent was then removed under reduced pressure. The residues were purified by column chromatography through a silica pad using 25 % ethyl acetate in *n*-heptane as the eluent. The resulting brown solid was further purified by chromatography over silica gel; using a 0 % to 25 % ethyl acetate in *n*-heptane gradient as the eluent. The solid was triturated

with *n*-heptane to give *N*2-(4-bromophenyl)-5-ethyl-1,3-benzoxazol-2-amine (0.96g, 0.003 mol, 46 %); RP-HPLC Rt 12.1 min, 99 % purity (DeltaPak® C18, 5 µm, 300 Å, 15 cm; 5%-95% acetonitrile/0.1M ammonium acetate over 10 min, 1mL/min); and *m/z* 317 and 319 (*MH*⁺).

5 **Example 8. N2-(4-Bromophenyl)-5-methyl-1,3-benzoxazol-2-amine**



2-Amino-4,6-dimethylphenol (0.214 g, 1.00 mmol) was added to a solution of 4-bromophenyl isothiocyanate (0.137 g, 1.00 mmol) in tetrahydrofuran (15 mL) and the reaction was stirred at room temperature for about 12 hours. Anhydrous copper (II) sulfate (1.50 g, 9.43 mmol), silica gel (1.50 g), and triethylamine (0.14 mL, 1.00 mmol) were added, and the mixture was stirred at room temperature for about another 16 hours. The reaction was filtered through a pad of diatomaceous earth, washed with additional tetrahydrofuran (2 x 20 mL), and the combined filtrate was concentrated under reduced pressure to afford *N*2-(4-bromophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine as a brown pink solid (0.30 g, 90 %); RP-HPLC Rt 17.395 min, 95% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak® C18, 300 Å, 5 µm, 150 x 3.9 mm column); ¹H NMR (400 MHz, *d*₆-DMSO) 2.33 (3H, *s*), 2.38 (3H, *s*), 6.79 (1H, *s*), 7.09 (1H, *s*), 7.54 (2H, *dd*, *J* 11.7 and 2.9 Hz), 7.72 (2H, *dd*, *J* 11.7 and 2.9 Hz) and 10.77 (1H, *s*).

20 **Examples detailing the range of reaction conditions for the synthesis of N2-(4-Bromophenyl)-5-methyl-1,3-benzoxazol-2-amine**

The following reaction conditions serve to illustrate the range of viable conditions and are not to be construed as limiting the scope of the present invention to the protocols exemplified.

25 **i). Optimization of ratios of reagents and temperature**

Examples 8.1 to 8.8

2-Amino-4,6-dimethylphenol (1-10 mmol) was added to a solution of a substituted 4-bromophenyl isothiocyanate (1 equivalent) in tetrahydrofuran (20-100 mL) and the reaction was stirred at room temperature for about 2-24 hours. Once the formation of the intermediate, *N*-(4-bromophenyl)-*N'*-(2-hydroxy-3,5-

30

dimethylphenyl)thiourea, was complete, anhydrous copper (II) sulfate (0-10 equivalents), silica gel (0-30 equivalents) and triethylamine (1 equivalent) were added and the reaction mixture was stirred at a temperature between about 20 and 60 °C for about 3-93 hours. The reaction was worked-up using one of the following procedures:

5 A. The reaction mixture was filtered through a pad of diatomaceous earth, washed with additional tetrahydrofuran (2 x 20 mL), and the combined filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (400 mL) and washed with one of the following:

A.1. 10% w/v aqueous EDTA (3 x 100 mL)

10 A.2. 10% v/v aqueous pyridine (3 x 100 mL)

A.3. 10% v/v aqueous ammonium hydroxide (28 to 30 % ammonia content)

(3 x 100 mL). The organic layer was then dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford *N2-(4-bromophenyl)-5-methyl-1,3-benzoxazol-2-amine* as a brown-pink solid

15 B. The reaction mixture was concentrated under reduced pressure then added to a silica pad. Purification by chromatography using 17 % ethyl acetate in *n*-heptane (2 L), followed by diethyl ether as the eluent gave *N2-(4-bromophenyl)-5-methyl-1,3-benzoxazol-2-amine*.

20 C. The reaction mixture was filtered through a pad of diatomaceous earth, washed with additional tetrahydrofuran (2 x 20 mL), and the combined filtrate was concentrated under reduced pressure to give *N2-(4-bromophenyl)-5-methyl-1,3-benzoxazol-2-amine*.

A summary of the results are detailed in Table 1.

Table 1. Examples of different reaction conditions and work-up protocols employed

Entry	Scale (mmol)	Equiv. of copper (II) sulfate	Equiv. of silica	Equiv. of triethylamine	Solvent	Temperature (°C)	Reaction time (h)	Work-up procedure	Isolated Yield (%) (HPLC purity) ((Cu content (ppm)))
8.1	2,4-Dimethyl-6-aminophenol (3.11)	9.43	30	1.0	THF	RT	24	A.1	72 % (94 % purity)
8.2	2,4-Dimethyl-6-aminophenol (3.11)	9.43	30	1.0	THF	RT	24	A.2	77 % (94 % purity) ((875 ppm))
8.3	2,4-Dimethyl-6-aminophenol (3.11)	9.43	30	1.0	THF	RT	24	A.3	74 % (94 % purity) ((708 ppm))
8.4	2,4-Dimethyl-6-aminophenol (2.13)	1.0	30	1.0	THF	RT	168	A.3	76 % (93 % purity)
8.5	2,4-Dimethyl-6-aminophenol (2.36)	1.1	0	1.0	CH ₃ CN	RT	27	A.3	70 % (> 99.5 % purity)
8.6	2,4-Dimethyl-6-aminophenol (2.36)	1.1	0	1.0	CH ₂ Cl ₂	RT	49	A.3	74 % (95 % purity)
8.7	2,4-Dimethyl-6-aminophenol (1.17)	1.1	0	1.0	THF	RT	49	A.3	70 % (87 % purity)
8.8	2,4-Dimethyl-6-aminophenol (1.17)	1.1	0	1.0	THF	60	3	A.3	99 % (91 % purity) ((178 ppm))

RP-HPLC conditions used: (5% to 85% acetonitrile/0.1M aqueous ammonium acetate,
 5 buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak® C18, 300 Å, 5 μ m,
 150 x 3.9 mm column).

ii). One-step one-pot processes

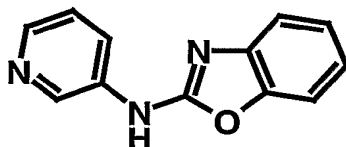
Example 8.9.

2-Amino-4,6-dimethylphenol (0.160 g, 1.17 mmol) anhydrous copper (II) sulfate (0.21 g, 1.29 mmol) and triethylamine (0.164 mL, 1.17 mmol) were added to a solution of 4-bromophenyl isothiocyanate (0.250 g, 1.17 mmol), in tetrahydrofuran (20 mL) and the reaction was stirred at room temperature for about 24 hours. The reaction was
5 filtered through a pad of diatomaceous earth, washed with ethyl acetate (2 x 20 mL), and the combined filtrate was concentrated under reduced pressure to afford *N2-(4-bromophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine* as a brown pink solid (0.33 g, 89 %); RP-HPLC Rt 17.294 min, 93% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm;
10 Deltapak® C18, 300 Å, 5 μ m, 150 x 3.9 mm column).

Example 8.10

Using the same scale and reaction procedure as detailed in Example 8.9, except that the reaction was stirred at about 60 °C for about 22 hours, *N2-(4-bromophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine* was afforded as a brown-pink solid (0.34 g, 91 %);
15 RP-HPLC Rt 17.268 min, 90% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak® C18, 300 Å, 5 μ m, 150 x 3.9 mm column).

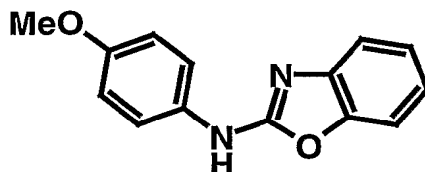
Example 9. *N2-(3-Pyridyl)-1,3-benzoxazol-2-amine*



20 3-Pyridyl isothiocyanate (0.311 g, 2.29 mmol) was added to a solution of 2-aminophenol (0.250 g, 2.29 mmol) in tetrahydrofuran (15 mL) and the reaction was stirred at room temperature for about 3 hours. Anhydrous copper (II) sulfate (0.410 g, 2.52 mmol) and triethylamine (0.32 mL, 2.29 mmol) were added, and the mixture was stirred at about 60 °C for about 96 hours. The reaction was filtered through a pad of
25 diatomaceous earth, the diatomaceous earth was washed with ethyl acetate (3 x 50 mL), and the combined filtrate was concentrated under reduced pressure. The residue was dissolved in methylene chloride (200 mL), washed with 10% v/v aqueous ammonium hydroxide (3 x 100 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford *N2-(3-pyridyl)-1,3-benzoxazol-2-amine* as a yellow
30 solid (0.343 g, 71 %); RP-HPLC Rt 9.580 min, 97% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at

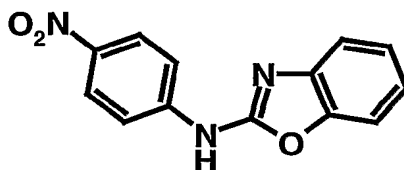
1 mL/min; $\lambda = 254$ nm; Deltapak® C18, 300 Å, 5 μ m, 150 x 3.9 mm column); ^1H NMR (400 MHz, d_6 -DMSO) 7.19 (1H, *m*), 7.24 (1H, *m*), 7.42 (1H, *m*), 7.48 (2H, *m*), 8.27 (2H, *m*), 8.87 (1H, *d*, *J* 2.3 Hz) and 10.87 (1H, *s*).

Example 10. N2-(4-Methoxyphenyl)-1,3-benzoxazol-2-amine



Using the protocol and scale described for the synthesis of Example 9. The cyclodesulfurization step was complete after about 72 hours at about 60 °C and purified in the same way as detailed in Example 9 to afford *N2-(4-methoxyphenyl)-1,3-benzoxazol-2-amine* as a brown solid (0.536 g, 97 %); RP-HPLC Rt 12.529 min, 94
purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1 mL/min; $\lambda = 254$ nm; Deltapak® C18, 300 Å, 5 μ m, 150 x 3.9 mm column); ^1H NMR (400 MHz, d_6 -DMSO) 3.75 (3H, *s*), 6.97 (2H, *dd*, *J* 6.9 and 2.2 Hz), 7.11 (1H, *dt*, *J* 6.5 and 1.1 Hz), 7.20 (1H, *dt*, *J* 6.5 and 1.1 Hz), 7.41 (1H, *dd*, *J* 7.7 and 0.6 Hz), 7.45 (1H, *dd*, *J* 7.7 and 0.6 Hz), 7.65 (2H, *dd*, *J* 6.9 and 2.2 Hz) and 10.38 (1H, *s*).

Example 11. N2-(4-Nitrophenyl)-1,3-benzoxazol-2-amine



Using the protocol and scale described for the synthesis of Example 9. The cyclodesulfurization step was complete after about 22 hours at about 60 °C and purified in the same way as detailed in Example 9 to afford *N2-(4-nitrophenyl)-1,3-benzoxazol-2-amine* as a yellow solid (0.409 g, 70 %); RP-HPLC Rt 13.876 min, > 99.9 % purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1 mL/min; $\lambda = 254$ nm; Deltapak® C18, 300 Å, 5 μ m, 150 x 3.9 mm column); ^1H NMR (400 MHz, d_6 -DMSO) 7.23 (1H, *m*), 7.28 (1H, *m*), 7.55 (2H, *m*), 7.99 (2H, *dd*, *J* 7.2 and 2.1 Hz), 8.30 (2H, *dd*, *J* 7.2 and 2.1 Hz) and 11.44 (1H, *s*).

Example 12: 5-Chloro-1,3-benzoxazol-2-amine

Anhydrous copper (II) sulfate (1.1 to 10 equivalents, preferably 1.1 equivalents) and triethylamine (1.0 to 10 equivalents, preferably 1.0 equivalents) are added to a solution of N-(5-chloro-2-hydroxyphenyl)thiourea (1 equivalent) in an organic solvent, for example tetrahydrofuran, dichloromethane, or acetonitrile, and the mixture is stirred, 5 between about 20 °C and 100 °C, until the formation of the benzoxazole is complete. The reaction is filtered through a pad of diatomaceous earth, washed with solvent, and the combined filtrate is washed with 10% v/v aqueous ammonium hydroxide, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford 5-chloro-1,3-benzoxazol-2-amine.

10 **Example 13: 2-{1-(2S,3R)-2-(2-Pyridyl)-3-(4-methoxyphenyl)pyrrolidinyl]-5-chlorobenzoxazole**

Reaction of (2S, 3R)-2-(2-pyridyl)-3-(4-methoxyphenyl)pyrrolidine (Yee *et al.*, J. Org. Chem., **63**(2), 326-330, (1998)) with 2-amino-4-chlorophenol (supplier: Aldrich, 1.0 equivalent), triethylamine (1 equivalent), carbon disulfide (1 equivalent), and 15 hydrogen peroxide (30 %, 1 equivalent) in tetrahydrofuran, under the conditions proposed by Li *et al.*, J. Org. Chem., **62**(13), 4539-4540, (1997), gives (2S, 3R)-N1-(5-chloro-1,3-benzoxazol-2-yl)-3-(4-methoxyphenyl)-2-(2-pyridyl)-1-pyrrolidinecarbothioamide.

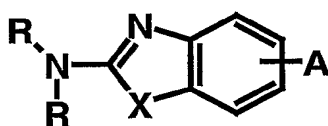
Anhydrous copper (II) sulfate (1.1 to 10 equivalents, preferably 1.1 equivalents) 20 and triethylamine (1.0 to 10 equivalents, preferably 1.0 equivalents) is added to a solution of (2S, 3R)-N1-(5-chloro-1,3-benzoxazol-2-yl)-3-(4-methoxyphenyl)-2-(2-pyridyl)-1-pyrrolidinecarbothioamide (1 equivalent) in an organic solvent, for example tetrahydrofuran, dichloromethane, or acetonitrile, and the mixture is stirred, between about 20 °C and 100 °C, until the formation of the benzoxazole was complete. The 25 reaction is filtered through a pad of diatomaceous earth, washed with solvent, and the combined filtrate is washed with 10% v/v aqueous ammonium hydroxide, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford 2-{1-(2S,3R)-2-(2-pyridyl)-3-(4-methoxyphenyl)pyrrolidinyl]-5-chlorobenzoxazole .

CLAIMS

What is claimed is:

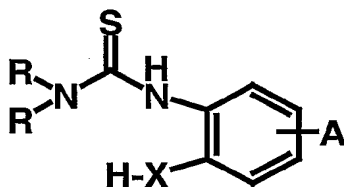
1. A method of making an optionally substituted 2-amino- benzoxazole or
 5 2-amino-benzimidazole which comprises reacting a corresponding optionally substituted
N-(2-hydroxyphenyl)thiourea or *N*-(2-aminophenyl)thiourea, respectively, with a
 transition metal in its I or II oxidation state, in the presence or absence of a base to
 obtain the optionally substituted 2-amino-benzoxazole or 2-aminobenzimidazole.

2. A process for the synthesis of a compound of formula (II),



(II)

comprising the step of reacting a compound of formula (I),



(I)

with a transition metal in its I or II oxidation state and optionally a base until the reaction
 is substantially complete to obtain the compound of formula (II);

wherein:

A represents one or more substituents, each independently selected from the group
 consisting of hydrogen, halogen, -CN, -NO₂, -C(O)OH, -C(O)H, and -OH, or is an
 optionally substituted moiety each independently selected from the group consisting of -
 C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heterocyclyl, -C(O)-alkyl, -C(O)-aryl, -C(O)-
 heterocyclyl, carboxamido, tetrazolyl, trifluoromethylcarbonylamino,
 trifluoromethylsulfonamido, alkyl, cycloalkyl, alkoxy, aryl, heterocyclyl, alkenyl,
 alkynyl, aryloxy, heterocyclyloxy, heterocyclylalkoxy, arylalkoxy, alkyl-S(O)_p-, alkyl-S-
 , aryl-S, heterocyclyl-S-, aryl-S(O)_p-, heterocyclyl-S(O)_p-, arylalkyl, heterocyclylalkyl,
 cycloalkylalkyl, amino, aminoalkyl, amido, -Z¹-C(O)N(R¹)₂, -Z¹-N(R¹)-C(O)-Z², -Z¹-
 25 N(R¹)-S(O)₂-Z², -Z¹-N(R¹)-C(O)-N(R¹)-Z², and CH₂OR²;

where R^1 for each occurrence is independently H, or optionally substituted alkyl, heterocyclyl, aryl, aralkyl or heterocyclalkyl;

p is 1 or 2;

R^2 for each occurrence is independently hydrogen, or optionally substituted alkyl, aryl, heterocyclyl, $-\text{CH}_2-\text{NR}^d\text{R}^e$, $-\text{W}-(\text{CH}_2)_t-\text{NR}^d\text{R}^e$, $-\text{W}-(\text{CH}_2)_t-\text{O}-\text{alkyl}$, $-\text{W}-(\text{CH}_2)_t-\text{S}-\text{alkyl}$, or $-\text{W}-(\text{CH}_2)_t-\text{OH}$;

R^d and R^e for each occurrence are independently H, alkyl, alkanoyl or SO_2 -alkyl; or R^d , R^e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

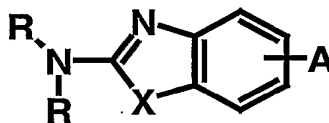
W is a covalent bond, O, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$ or NR^f , where R^f is H or alkyl; t for each occurrence is independently an integer from 2 to 6;

Z^1 is a covalent bond or alkyl;

Z^2 is an optionally substituted alkyl, aryl, heterocyclyl, arylalkyl, or heterocyclalkyl;

R for each occurrence is independently hydrogen or silyl or is independently an optionally substituted moiety selected from the group consisting of alkyl, arylalkyl, heterocyclalkyl, aryl, heterocyclyl, cycloalkyl, and cycloalkylalkyl; or each R is taken together with the nitrogen atom to which they are attached to form an optionally substituted 5- or 6-membered ring optionally having one or more other heteroatoms selected from the group consisting of N, O and S; and X is O, NH, N-alkyl, N-cycloalkyl, N-arylalkyl, N-heterocyclalkyl, N-sulfonyl, N-carboxyl, N-aryl, or N-heterocyclyl wherein the group attached to the nitrogen is optionally substituted with one or more substituents.

3. A process for the synthesis of a compound of formula (II),



(II)

comprising the step of reacting an isothiocyanate, an optionally substituted 2-(X)-aniline, a transition metal in its I or II oxidation state and optionally a base, until the reaction is substantially complete to obtain a compound of formula (II) wherein

A represents one or more substituents, each independently selected from the group consisting of hydrogen, halogen, -CN, -NO₂, -C(O)OH, -C(O)H, and -OH, or is an optionally substituted moiety each independently selected from the group consisting of -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heterocyclyl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heterocyclyl, carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, alkyl, cycloalkyl, alkoxy, aryl, heterocyclyl, alkenyl, alkynyl, aryloxy, heterocyclioxy, heterocyclylalkoxy, arylalkoxy, alkyl-S(O)_p-, alkyl-S-, aryl-S, heterocyclyl-S-, aryl-S(O)_p-, heterocyclyl-S(O)_p-, arylalkyl, heterocyclylalkyl, cycloalkylalkyl, amino, aminoalkyl, amido, -Z¹-C(O)N(R¹)₂, -Z¹-N(R¹)-C(O)-Z², -Z¹-N(R¹)-S(O)₂-Z², -Z¹-N(R¹)-C(O)-N(R¹)-Z², and CH₂OR²;

where R¹ for each occurrence is independently H, or optionally substituted alkyl, heterocyclyl, aryl, aralkyl or heterocyclylalkyl;

p is 1 or 2;

R² for each occurrence is independently hydrogen, or optionally substituted alkyl, aryl, heterocyclyl, -CH₂-NR^dR^e, -W-(CH₂)_t-NR^dR^e, -W-(CH₂)_t-O-alkyl, -W-(CH₂)_t-S-alkyl, or -W-(CH₂)_t-OH;

R^d and R^e for each occurrence are independently H, alkyl, alkanoyl or SO₂-alkyl; or R^d, R^e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

W is a covalent bond, O, S, S(O), S(O)₂ or NR^f, where R^f is H or alkyl; t for each occurrence is independently an integer from 2 to 6;

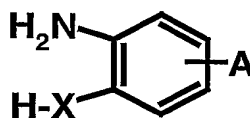
Z¹ is a covalent bond or alkyl;

Z² is an optionally substituted alkyl, aryl, heterocyclyl, arylalkyl, or heterocyclylalkyl;

R for each occurrence is independently hydrogen or silyl or is independently an optionally substituted moiety selected from the group consisting of alkyl, arylalkyl, heterocyclylalkyl, aryl, heterocyclyl, cycloalkyl, and cycloalkylalkyl; or each R is taken together with the nitrogen atom to which they are attached to form an optionally substituted 5- or 6-membered ring optionally having one or more other heteroatoms selected from the group consisting of N, O and S; and

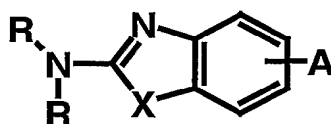
X is O, NH, N-alkyl, N-cycloalkyl, N-arylalkyl, N-heterocyclylalkyl, N-sulfonyl, N-carboxyl, N-aryl, or N-heterocyclyl wherein the group attached to the nitrogen is optionally substituted with one or more substituents.

4. A process according to claim 3 wherein the isothiocyanate is of the formula R-NCS and the optionally substituted aniline is of the formula



(I)

5. A process for the synthesis of a compound of formula (II),



(II)

5

comprising the steps:

forming an isothiocyanate *in situ* by reacting an amine or an aniline with a reagent having a thiocarbonyl moiety and which is capable of a double nucleophilic attack at the carbon of the thiocarbonyl moiety to yield the isothiocyanate;

10 reacting the isothiocyanate with an optionally substituted 2-(X)-aniline, a transition metal in its I or II oxidation state and optionally a base, until the reaction is substantially complete to obtain a compound of formula (II),

wherein

A represents one or more substituents, each independently selected from the group consisting of hydrogen, halogen, -CN, -NO₂, -C(O)OH, -C(O)H, and -OH, or is an
 15 optionally substituted moiety each independently selected from the group consisting of -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heterocyclyl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heterocyclyl, carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, alkyl, cycloalkyl, alkoxy, aryl, heterocyclyl, alkenyl,
 20 alkynyl, aryloxy, heterocycliloxy, heterocyclylalkoxy, arylalkoxy, alkyl-S(O)_p-, alkyl-S-, aryl-S, heterocyclyl-S-, aryl-S(O)_p-, heterocyclyl-S(O)_p-, arylalkyl, heterocyclylalkyl, cycloalkylalkyl, amino, aminoalkyl, amido, -Z¹-C(O)N(R¹)₂, -Z¹-N(R¹)-C(O)-Z², -Z¹-N(R¹)-S(O)₂-Z², -Z¹-N(R¹)-C(O)-N(R¹)-Z², and CH₂OR²;

where R¹ for each occurrence is independently H, or optionally substituted alkyl,

25 heterocyclyl, aryl, aralkyl or heterocyclylalkyl;

p is 1 or 2;

R^2 for each occurrence is independently hydrogen, or optionally substituted alkyl, aryl, heterocyclyl, $-CH_2-NR^dR^e$, $-W-(CH_2)_t-NR^dR^e$, $-W-(CH_2)_t-O-alkyl$, $-W-(CH_2)_t-S-alkyl$, or $-W-(CH_2)_t-OH$;

R^d and R^e for each occurrence are independently H, alkyl, alkanoyl or $SO_2-alkyl$; or R^d , R^e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

W is a covalent bond, O, S, $S(O)$, $S(O)_2$ or NR^f , where R^f is H or alkyl;

t for each occurrence is independently an integer from 2 to 6;

Z^1 is a covalent bond or alkyl;

Z^2 is an optionally substituted alkyl, aryl, heterocyclyl, arylalkyl, or heterocyclylalkyl;

R for each occurrence is independently hydrogen or silyl or is independently an optionally substituted moiety selected from the group consisting of alkyl, arylalkyl, heterocyclylalkyl, aryl, heterocyclyl, cycloalkyl, and cycloalkylalkyl; or each R is taken together with the nitrogen atom to which they are attached to form an optionally substituted 5- or 6-membered ring optionally having one or more other heteroatoms selected from the group consisting of N, O and S; and

X is O, NH, N-alkyl, N-cycloalkyl, N-arylalkyl, N-heterocyclylalkyl, N-sulfonyl, N-carboxyl, N-aryl, or N-heterocyclyl wherein the group attached to the nitrogen is optionally substituted with one or more substituents.

6. The process according to claim 1, 2, 3, 4 or 5, wherein the base is present.

7. The process according to claim 6, wherein the transition metal is Cr, Mn, Fe, Co, Cu or Zn, or a combination thereof.

8. The process according to claim 7, wherein the transition metal is a corresponding salt or a combination of salts.

9. The process according to claim 8, wherein the transition metal salt is one or more copper salts.

10. The process according to claim 9, wherein the copper salt is copper (II) sulfate, anhydrous copper (II) sulfate or copper (I) chloride, or a combination thereof.

11. The process according to claim 6, wherein the base is one or more organic bases.

12. The process according to claim 11, wherein the organic base is triethylamine or ammonia, or a combination thereof.

13. The process according to claim 12, wherein the transition metal is copper (II) sulfate, anhydrous copper (II) sulfate or copper (I) chloride, or a combination thereof.

14. The process according to claim 6, wherein the base is one or more
5 inorganic bases.

15. The process according to claim 14, wherein the inorganic base is sodium hydroxide, sodium hydrogen carbonate or cesium carbonate, or a combination thereof.

16. The process according to claim 15, wherein the transition metal is copper (II) sulfate, anhydrous copper (II) sulfate or copper (I) chloride, or a combination
10 thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/08910

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : CO7D 263/54, 413/02

US CL : 548/222, 306.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/222, 306.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN CAS ONLINE, EAST**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SATO et al, Benzoxazole derivatives as novel 5-HT ₃ receptor partial agonists in the gut. J. Med. Chem. 1998, Vol. 41, pages 3015-3021, especially page 3016-3017.	1-16
A	US 5,856,107 A (OSTRESH et al) 5 January 1999 (05.01.1999), column 12-19	1-16
A	US 4,064,136 (LOEW et al) 20 December 1977 (20.12.1977), column 4-7.	1-16
A	US 3,873,558 (GRENDAL et al) 25 March 1975 (25.03.1975), column 3-5.	1-16

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

19 June 2002 (19.06.2002)

Date of mailing of the international search report

12 JUL 2002

Name and mailing address of the ISA/US

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